REMARKS/ARGUMENTS

I. Amendments

Claims 1-4, 7-9, 19-34 and 36-39 are pending in the application. All of the pending claims are currently rejected by the Examiner under 35 U.S.C. 112, first paragraph, as not enabled. In this Amendment, Applicants have canceled claims 2-4 and 7-9. Claim 1 has been amended to incorporate the limitations recited in canceled claims 2-4, 7 and 8 (which were dependent on claim 1), and also to recite a step of administering the vector to a cancer cell (*in vivo* or *ex vivo*) by directly injecting the recombinant vectors into a tumor comprising the cancer cell. Support for the amendments to claim 1 can be found, *e.g.*, in the claims as originally filed and in the specification at page 6, lines 1-9; page 20, line 21 to page 21, line 11; and page 22, line 29 to page 23, line 1. Independent claim 19 has been amended to recite a substantial utility for the claimed vector composition: expression of an interferon-α polypeptide in a mammalian cell. Support for this amendment can be found in the claims as originally filed. Claim 34 has been amended to recite methods for inhibiting (not necessarily killing) the growth of hepatocellular carcinoma cells in which interferon-α lacking a secretion leader sequence is expressed, and also to recite a step of administering the vector to a cancer cell (*In vivo* or *ex vivo*) by directly injecting the recombinant vectors into a tumor comprising the cancer cell. Support for the amendments to claim 34 can be found, *e.g.*, in the claims as originally filed and in the specification at page 6, lines 1-9; page 20, line 21 to page 21, line 11; and page 22, line 29 to page 23, line 1.

Applicants have amended their claims without prejudice and expressly reserve the right to pursue claims of equal or greater scope in this application or in a related application. No new matter has been added to any of the pending claims. For the reasons set forth herein, Applicants believe that the each of the Examiner's enablement rejections is overcome.[1]

[1] Applicants and Examiner discussed several of the issues discussed herein during a brief telephonic Interview on August 25, 2004. Although agreement was not reached with respect to the allowability of the previously pending claims, Applicants greatly appreciate the thoughtful comments provided by the Examiner and the Examiner's generous donation of her time.

II. Enablement of Pending Composition Claims 19-33 Under 35 U.S.C. 112[2]

A patentable composition needs only one enabled use. *See* 35 U.S.C. 101; *see also Raytheon v. Roper*, 724 F.2d 951 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 835 (1984). The MPEP explains that this use must be specific, substantial and credible. *See* MPEP 2164.07. Here, Applicants' claimed compositions have a specific, substantial and credible use: they are useful for expressing interferon-α polypeptides lacking secretion leader sequences in mammalian cells. This utility is recited explicitly in Applicants' amended claims.

Applicants' recited utility is specific, substantial and credible because Applicants have identified a "particular biological activity" for the non-secreted interferon-α polypeptides encoded by their vector and explained how that activity can be utilized by those of skill in the art. *See* MPEP 2107.02.II.A. The anti-proliferative and antiviral properties of non-secreted interferon-α are demonstrated in Figures 4 and 5 of the specification (*see* specification at page 4, lines 19-28). Moreover, the experimental results depicted in Figures 5-8 show that non-secreted interferon-α polypeptides exhibit the biological activity of their secreted counterparts and are equally capable of inducing biologically relevant activities including the phosphorylation of STAT1 and hypophosphorylation of Rb.

The biologically active non-secreted interferon-α proteins encoded by Applicants' claimed vectors can be expressed "in a variety of recombinantly engineered cells," as disclosed by Applicants on page 16, lines 12-15 of the specification. Based on Applicants' disclosure, the specified utility of a vector capable of expressing biologically active non-secreted interferon-α polypeptides is clearly credible, *i.e.*, one of ordinary skill in the art would believe in such a utility. *See* MPEP 2107.02.III.B.

Applicants also note that, in addition to the explicitly provided utility, other specific, substantial and credible utilities of a vector capable of expressing a biologically active interferon-α polypeptide need not be explicitly disclosed when the utility is well-established. *See* MPEP 2107.02.II.B, citing *In re Folkers*, 344 F.2d 970 (CCPA 1965). Section 2107.02.II.B of

[2] Because of the different issues presented, Applicants will deal with the enablement of the pending composition claims separately from the pending method claims.

the MPEP provides "the cloning and characterization of the nucleotide sequence of a well-known protein such as insulin" as an example of a composition with a well-established utility. Similarly, Applicants have not only cloned and characterized vectors encoding a non-secreted interferon-α polypeptide, but they have demonstrated (as discussed above) that the biological activity of the expressed protein is identical for practical purposes to that of secreted interferon-α polypeptides. As of the priority date of Applicants' application, the utility of purified interferon-α polypeptides which were biologically active in mammalian systems was well-recognized. For instance, it was well-known that interferon-α polypeptide could be administered therapeutically to patients with myeloproliferative disorders *(see, e.g.*, the studies cited in the "Background" section of Applicant's specification at page 1, line 17 to page 2, line 5). Thus, the utility of a vector capable of *expressing* an interferon-α peptide in a mammalian cell need not be explicitly disclosed for the utility of such a vector to be recognized by one of ordinary skill in the art. A non-secreted interferon-α polypeptide expressed from Applicants' claimed vectors in mammalian cells is very likely to be folded and processed correctly for maximum activity and, based on Applicants' disclosure, this advantage would be recognized by one skilled in the art. Non-secreted interferon-α polypeptide expressed from Applicants' claimed vectors in mammalian cells could be purified according to any of several methods well-known to those of ordinary skill.[3] As stated above, only *one* specific, substantial and credible utility for a composition needs to be enabled for patentability purposes. Applicants have discovered novel vectors which are useful for expressing biologically active and non-secreted interferon-α polypeptides. Whether Applicants' have taught one of skill in the art how to successfully cure cancer with their vectors is therefore *irrelevant* to the discussion of whether their compositions are, in fact, patentably enabled (*see, e.g.*, MPEP 2107.02.I ("[I]f Applicant makes one credible assertion of utility, utility for the claimed invention as a whole is established"), citing *In re Gottlieb*, 328 F.2d 1016 (CCPA 1964) ("Having found that the antibiotic is useful for some

[3] Applicants submit that enablement of this utility does not require extraordinary or even commercial levels of the protein to be expressed in the cells. Enough protein is expressed that a biochemist of ordinary skill can measure the biological activity of the extracts and purify it to levels that are appropriate for whatever use is envisioned by the biochemist.

purpose, it becomes unnecessary to decide whether it is in fact useful for the other purposes 'indicated' in the specification ...")).

Based on what was known in the art at the time of filing, and in light of what is taught in their specification, Applicants have provided more than sufficient teaching for one of ordinary skill to make and use their recombinant vectors for the expression of non-secreted interferon-α polypeptides which are biologically active in mammalian cells.[4] Applicants submit that the enablement of vectors with the recited utility is supported by the results in the Figures described above and additional experiments *in vivo*. Applicants have taught how to use and test the vectors in the specification at, *e.g.*, Examples 4-8. Moreover, Applicants have demonstrated that their constructs, when injected into hepatocellular tumors in mice, express non-secreted interferon-α which causes those tumors to shrink dramatically *(see* specification at page 20, line 21 to page 21, line 11; Figure 10). Applicants submit that one of ordinary skill would recognize that the methods for making and using the claimed vectors are taught and the biological activity of the non-secreted interferon-α expressed is clearly established. For all the forgoing reasons, the Examiner should withdraw the rejection of Applicants' composition claims under 35 U.S.C. § 112, first paragraph.

Arguments relevant to the enablement of other uses of the vector are discussed below.

III. Enablement of Pending Method Claims 1 and 34-39

The Examiner rejected all of Applicants' pending method claims as being non-enabled. Applicants have amended the previously pending claims. As amended, the claims describe embodiments of Applicants' invention that have not previously been subjected to the Examiner's analysis under 35 U.S.C. 112, first paragraph. Specifically, the amended claims recite methods for expressing interferon-α polypeptides using techniques of direct injection which, together with the use of tissue-specific promoters, greatly diminishes any alleged

[4] Or, to paraphrase the Examiner, Applicants have shown the skilled artisan "how to make the necessary starting materials and ... how to use them to produce the biological effects *as recited in the claims*." *See* January 29, 2004 Office Action at page 3 *(emphasis added)*.

unpredictability and/or safety issues associated with the use of the methods in "gene therapy" applications, *e.g.*, allergic reactions, inappropriate expression, etc. Applicants also note that the claims do not require the "curing" or "destroying" or "killing" of any and all cancerous cells in an animal which might be treated with their claimed method. In addition, the claimed methods may be practiced in conjunction with other methods for effecting anti-proliferation of cells, including those methods described in the specification and other methods known to those of ordinary skill in the art. *See, e.g.*, page 22, lines 21-25 (describing immunosuppressive agents which may be administered with the vectors recited in the claimed methods); page 23, line 23 to page 24, line 12 (describing delivery enhancing agents); and page 25, lines 21-27 (describing *ex vivo* administration to cells or tissues).

The Examiner has expressed doubt that studies showing the successful use of recombinant vectors to treat tumors in xenograft animal models is sufficiently predictive to meet the enablement standard. Applicants disclosed the results of such a study in their specification (*e.g.*, Figure 10). Applicants respectfully submit that the use of xenograft mice (*e.g.*, BALBC nuce mice) to determine whether a test compound is likely to be effective in other animals (*e.g.*, cats, dogs, livestock and humans) is widespread and has been so for years, dating back to at least Applicants' priority date.

With respect to the level of skill required to practice Applicants' claims, Applicants' do not understand the distinction that the Examiner appears to be drawing between artisans with an exceptionally high level of expertise and artisans with exceptional skill. As of Applicants' filing date, there were many skilled practitioners capable of following protocols and performing the routine experimentation -- manipulation of virus titers, identification of tumor cells likely to be targetable, *etc.* -- required to successfully practice Applicants' claimed methods. For example, as early as 1994, effective peritumoral delivery of adenoviruses encoding p53 was demonstrated by Wills et al. (*Human Gene Therapy*, *5*:1079, 1081 (1994)) (copy enclosed). Those skilled in the art were aware of this work and their ability to practice the necessary protocols is presumed.

In an earlier Office Action (paper 5), the Examiner cited Gura's 1997 article and quoted Alan Oliff stating that "[animal] model systems are not predictive at all." Applicants note

that in spite of this titillating soundbite, Dr. Oliff continued to regularly direct and publish animal experiments evaluating cancer treatments using xenograft models (a list of seven such articles is attached). Applicants respectfully submit that Dr. Oliff does not continue to use xenograft animal models merely to prove that such models are worthless to scientists. Moreover, the FDA appears to disagree strongly with Dr. Oliff, as the FDA relies heavily on data obtained from such models when evaluating the efficacy and safety of proposed therapeutics.

Throughout the Office Actions, the Examiner has expressed concern that studies using immunocompromised mice such as those described in Applicants' specification (*e.g.*, Figure 10) do not reflect the results that would be observed with immunocompetent mice. Applicants recognize that immunocompromised mice and immunocompetent mice differ in important ways, but respectfully submit that the non-secreted interferon-α polypeptides encoded by Applicants' vector would not be expected to be any more immunogenic than the well-studied secreted form of the protein. The Examiner's position appears to be that a preexisting or induced immune response to an adenoviral vector would render the vector useless upon systemic application. As an initial matter, Applicants' submit that this is essentially an issue of bioavailability which is commonly dealt with in the pharmaceutical field by dosage regimen. So long as the dose sufficient to provide a response is lower than the toxic dose, the agent can exert its therapeutic effect, however small. Applicants' have provided in their previous communications a wealth of evidence that systemic application of adenoviruses does not prevent efficacy. That evidence points to a clear conclusion: the fact that an agent may induce an immune response does not preclude its efficacy.

Applicants have also attached an unpublished but submitted paper by Tsai *et al.* (copy attached) which shows that the replication-deficient (protein IV-deleted) adenovirus vectors recited in Applicants' achieved anti-tumor efficacy in the presence of a pre-existing blocking titer of human anti-adenovirus antibodies. *See, e.g.*, page 4, first full paragraph; pages 4, "Adenovirus vectors"; and page 9, "Effect of human neutralizing antibodies on adenovirus vector function ...." Thus, Applicants submit that their studies using a nude mouse model are predictive and do not differ significantly from results which would be obtained in an "immunocompetent" mouse. This work was specifically designed to address what appears to be

the Examiner's concern: the potential neutralization of systemically administered adenoviruses by a pre-existing immune response. As shown by the data provided in this work, the presence of pre-existing or induced anti-adenoviral antibodies does not preclude the ability of systemically administered adenovirus to cause an antitumor effect in these animal models.

Additionally, the Examiner may question the mouse xenograft model for the evaluation of human adenovirus vectors as predictive of the effects of such vectors when administered to human beings since the human adenovirus vectors preferentially infect human cells leaving much of the mouse privileged from infection by the adenoviral agent. Such an argument is plausible – except for the fact that the human experience in clinical trials with a wide variety of adenoviral vectors has demonstrated a correlation between the effects demonstrated in the preclinical models and the clinical experience and a lack of toxicity associated with these agents. Such an argument could be advanced with respect to any therapeutic compound. If preclinical models were always predictive of the human condition, no compounds would ever fail in the clinic. No animal model is perfectly predictive of the response in the human being but there is sufficient correlation of such models to the human condition for one of skill in the art to believe that agent which demonstrate activity in such models will likely have activity in human beings. The courts have repeatedly held and the USPTO has expressly adopted the policy that human clinical data is not required for enablement of compositions or methods which may be useful for treating human diseases.

In Paper 5, the Examiner also cited the Marshall article for the proposition that "the central challenge in the field of gene therapy is to find safe vectors capable of transporting genes efficiently into target cells and getting the cells to express the genes once they are inserted." *See* Paper 5, page 6. Applicants remind the Examiner that Applicants' pending claims are not drawn to encompass the entire field of adenovirus based gene therapy and Applicants do not pretend to have enabled a gene-based cure for every human disease.

The Marshall article chronicles the discovery of leukemia in children receiving retroviral gene therapy for X-linked severe combined immunodeficiency (X-SCID). Applicants submit that the Marshall article does not show that those skilled in the art of developing recombinant adenovirus treatments for cancer cannot reasonably predict whether a particular

construct will have any functionality or effectiveness in a clinical setting. Rather, the articles demonstrate only that treating certain particularly severe *genetic diseases* with the retrovirus-based or adenovirus-based protocols described in the articles is accompanied by serious risks. Applicants remind the Examiner that *nearly all* existing methods of treating tumors with pharmaceuticals are accompanied by the risk of serious, often life-shortening, side-effects. To the extent that the absence of any risk is neither explicitly nor implicitly included in the pending claims, the Examiner's implicit reliance on such risks to reject the pending claims is misplaced and contrary to law. *See, e.g., Scott v. Finney*, 34 F.3d 1058, 1063 (Fed. Cir. 1994) ("Testing for full safety and effectiveness . . . is more properly left to the [FDA].").[5]

Applicants also respectfully draw the Examiner's attention to an apparent double-standard in the Patent Office's approach to these issues. In 1997, David T. Curiel filed an application for a U.S. patent with claims reciting methods for transducing cells with replication-deficient adenoviral vectors. The purpose of the methods as stated in the specification of Dr. Curiel's patent is to allow "effective genetic correction in the context of gene therapy." The patent (U.S. Patent No. 6,333,030) issued Christmas Day, 2001. The Examples provided in Dr. Curiel's patent specification describe the transduction of a xenografted tumor in mice and Applicants' pending claims appear to be of similar scope to those issued to Dr. Curiel. Dr. Curiel did *not* provide any clinical data in the patent specification or by declaration during prosecution. Thus, Dr. Curiel's implicit opinion that, at least as early as 1997, xenografted tumors were useful for predicting adenovirus-based treatments in humans was shared by the Patent Office at least as recently as Christmas Day, 2001. Applicants recognize that the decisions of the Patent Office with respect to the allowance of another's claims are not binding on all parties. Nevertheless, Applicants remain puzzled by the seemingly contradictory approach taken by the Patent Office with respect to the efficacy, predictability and enablement of "gene therapy" claims.

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[5] Applicants also wish to point out that the FDA's requirements for "safety" and predictability are often higher than that deemed acceptable to scientists and medical practitioners seeking to treat terminally ill people who have no other alternatives. *See, e.g.,* Bailey, R., *ReasonOnline*, "Timid Bureaucrats Kill People," (Jan. 9, 2002) (copy attached).

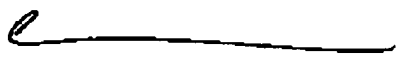
In summary, Applicants' position is that, in light of their teaching and the knowledge of those skilled in the art, the use of Applicants' *xenograft-proven* recombinant adenovirus is *reasonably likely* to (1) successfully express the encoded interferon-α polypeptide and (2) effectively diminish the growth of at least *some* transfected tumor cells in the targeted population, without undue experimentation. Applicants' respectfully submit that to satisfy the enablement requirement they need not prove that the *risk-free elimination* of tumors occurs inevitably when their claimed methods are practiced.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



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